

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>5780-01-TMC</b>	<b>FOR FURTHER ACTION</b>		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. <b>PCT/US 98/ 23992</b>	International filing date (day/month/year) <b>10/11/1998</b>	(Earliest) Priority Date (day/month/year) <b>17/11/1997</b>	
Applicant  <b>WARNER-LAMBERT COMPANY et al.</b>			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23992

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C07K14/47 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17213 A (SLOAN KETTERING INST CANCER) 29 June 1995	1
A	see page 21 - page 26 see figures 1A and 1B	2-4
X	BIAN ET AL: "Characterisation of a putative p53 binding site in the promoter of the mouse tissue inhibitor of metalloproteinases-3 (TIMP-3) gene: TIMP-3 is not a p53 target gene" CARCINOGENESIS, vol. 17, no. 12, 1996, pages 2559-2562, XP002098171 cited in the application	2,3
A	see abstract see page 2560, right-hand column, paragraph 2 - page 2561, left-hand column, line 4	1,4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 March 1999

Date of mailing of the international search report

13/04/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Jansen, K-S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KAGHAD ET AL: "Monoallelically Expressed Gene Related to p53 at 1p36, a Region Frequently Deleted in Neuroblastoma and Other Human Cancers" CELL, vol. 90, 22 August 1997, pages 809-819, XP002098172 cited in the application see abstract ---	1
A	EL-DEIRY ET AL: "Definition of a consensus binding site for p53" NATURE GENETICS, vol. 1, 1992, pages 45-49, XP002098173 cited in the application ---	2-4
A	WO 96 01907 A (SQUIBB BRISTOL MYERS CO) 25 January 1996 see page 38, SEQ ID NO.:3 ---	4
P,X	BIAN AND SUN: "p53CP, a putative p53 competing protein that specifically binds to the consensus p53 DNA binding sites: A third member of the p53 family?" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 94, December 1997, pages 14753-14758, XP002098174 see the whole document -----	1-4

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23992

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9517213	A	29-06-1995	AU	1440695 A	10-07-1995
WO 9601907	A	25-01-1996	US	5667987 A	16-09-1997
			EP	0804609 A	05-11-1997

## PATENT COOPERATION TREATY

## PCT

21 FEB 2000

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD-5780-01-TMC		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) <b>FOR FURTHER ACTION</b>
International application No. PCT/US98/23992	International filing date (day/month/year) 10/11/1998	Priority date (day/month/year) 17/11/1997
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 19/05/1999	Date of completion of this report 15.02.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kalsner, I Telephone No. +49 89 2399 8708 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/23992

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-27 as originally filed

### Claims, No.:

1-4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/23992

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

### 2. Citations and explanations

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**se separate sh t**

**Ad Section IV: Lack of unity of invention**

An international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same special technical features, special technical features being such features that define a contribution over which each of the claimed inventions, considered as a whole, makes over the prior art.

The only possible technical feature which could be regarded as being common to the subject-matter of claims 1-4 is the consensus p53 binding site which the protein of claim 1 binds to and which is comprised in the DNA sequences of claims 2-3.

This consensus binding site, however, is known in the state of the art (see e.g. D1).

Therefore the protein of claim 1 and the different DNA fragments of claims 2-4 are no longer linked by a common new and inventive concept. The application, thus falls apart into 4 different inventions each claim representing one independent invention.

As the examination of the present application can be carried out without undue effort, the IPEA chooses, according to Rule 68.1 PCT, not to invite the applicant to restrict or pay additional examination fees.

**Ad Section V: Reasoned statement with regard to novelty, inventive step or industrial applicability**

**1) Documents**

D1...WO-A-9517213

D2...Bian et al. (1996) Carcinogenesis 17: 2559-2562

**2) Novelty**

2.1) **Claim 1** does not meet the requirements of Art. 33 PCT in view of D1. D1



discloses fragments of p53 generated by subtilisin digestion. It shows that different cleavage sites of the protein are susceptible to different enzyme concentrations (p. 21, last par.). An approximately 40 kDa fragment of p53 which includes the consensus binding sites is e.g. the fragment derived from cleavage at positions 8, 18 or 23 and 305 or 311.

D1 is thus considered to take away novelty of **claim 1**.

- 2.2) The isolated DNA fragments comprising the sequences SEQ ID NO: 8 (claim 2) or SEQ ID NO: 10 (claim 3) are disclosed in D2 (p. 2560, right col., lines 32/33 [T3SF]).

**Claims 2 and 3**, thus cannot be considered novel in view of D2.

- 2.3) **Claim 4** meets the requirements of Art. 33(2) PCT as the sequence as such is not disclosed in any of the available prior art.

### **3) Inventive step**

**Claim 4** does not meet the requirements of Art. 33(3) PCT for the following reason:

**Claim 4** is directed to an isolated DNA fragment which comprises a repeat of one of the known motives of the p53 binding site. Since there is no indication in the description of the significance of this particular sequence the provision of a DNA fragment comprising two such motives linked together does not involve an inventive step.

### **4) Priority**

The validity of the priority date of the present application has not been checked. If, however, the claimed priority is not valid, the documents cited in the International Search Report as "P" (Bian & Sun, 1997, PNAS 94: 14753-14758) would be relevant for assessment of novelty and inventive step of the present set of claims.

**Ad Section VII: Certain defects in the international application**

Drawings have not been filed with the application. The references to the figures, therefore, have to be deleted from the description.

**Ad Section VIII: Certain observations on the international application**

**Claim 1** does not meet the requirements of Art. 6 PCT as the protein claimed is merely defined by its approximate molecular weight and by a functional feature. Claims, however should be defined by technical (=structural) features in order for the skilled person to unambiguously distinguish the claimed subject-matter from the prior art.

**Claim 4** is not considered to meet the requirements of Art. 5 and 6 PCT as the specific sequence and its significance is not mentioned in the description.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

WARNER-LAMBERT COMPANY  
Attn. RYAN, A.  
201 Tabor Road  
Morris Plains, New Jersey 07950  
UNITED STATES OF AMERICA

COMMUNICATION IN CASES FOR WHICH  
NO OTHER FORM IS APPLICABLE

Date of mailing  
(day/month/year) 23/04/1999

Applicant's or agent's file reference

5780-01-TMC

REPLY DUE

See paragraph 1 below

International application No.

PCT/US 98/ 23992

International filing date  
(day/month/year)

10/11/1998

Applicant

WARNER-LAMBERT COMPANY et al.

1. ☐ REPLY DUE within \_\_\_\_\_ ~~XXXX~~ days from the above date of mailing

☒ NO REPLY DUE

## 2. COMMUNICATION:

We refer to the International Search Report sent to you on March 13th, 1999.

Please be informed that the Abstract has been subsequently Modified.

We therefore enclose a new and complete Search Report which cancels and replaces the one already in your possession.

A copy of this letter and the new Search Report has been sent to the International Bureau of W.I.P.O.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Andria Overbeeke-Siepkens

## B x III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

p53 Tumor suppressor protein negatively regulates cell growth, mainly through the transactivation of its downstream target genes. As a sequence specific DNA binding transcriptional factor, p53 specifically binds to a 20 bp consensus motif 5'-PuPuPuC(A/T)(T/A)GPyPyPuPuPuC(A/T)(T/A)GPyPyPy-3'. We have now identified, partially purified and characterized an additional nuclear protein, p53CP (p53 competing protein) that specifically binds to consensus p53 binding sites found in several p53 downstream target genes including Waf-1, Gadd45, Mdm-2, Bax, and RGC.

## INTERNATIONAL SEARCH REPORT

International Application No

T/US 98/23992

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C07K14/47 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 17213 A (SLOAN KETTERING INST CANCER) 29 June 1995	1
A	see page 21 - page 26 see figures 1A and 1B	2-4
X	--- BIAN ET AL: "Characterisation of a putative p53 binding site in the promoter of the mouse tissue inhibitor of metalloproteinases-3 (TIMP-3) gene: TIMP-3 is not a p53 target gene" CARCINOGENESIS, vol. 17, no. 12, 1996, pages 2559-2562, XP002098171 cited in the application	2,3
A	see abstract see page 2560, right-hand column, paragraph 2 - page 2561, left-hand column, line 4 ---	1,4
	-/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

20 April 1999

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Jansen, K-S

## INTERNATIONAL SEARCH REPORT

International Application No

T/US 98/23992

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KAGHAD ET AL: "Monoallelically Expressed Gene Related to p53 at 1p36, a Region Frequently Deleted in Neuroblastoma and Other Human Cancers" CELL, vol. 90, 22 August 1997, pages 809-819, XP002098172 cited in the application see abstract ---	1
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A	WO 96 01907 A (SQUIBB BRISTOL MYERS CO) 25 January 1996 see page 38, SEQ ID NO.:3 ---	4
P,X	BIAN AND SUN: "p53CP, a putative p53 competing protein that specifically binds to the consensus p53 DNA binding sites: A third member of the p53 family?" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 94, December 1997, pages 14753-14758, XP002098174 see the whole document -----	1-4

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 98/23992

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9517213	A	29-06-1995	AU	1440695 A	10-07-1995
WO 9601907	A	25-01-1996	US	5667987 A	16-09-1997
			EP	0804609 A	05-11-1997
			US	5886149 A	23-03-1999

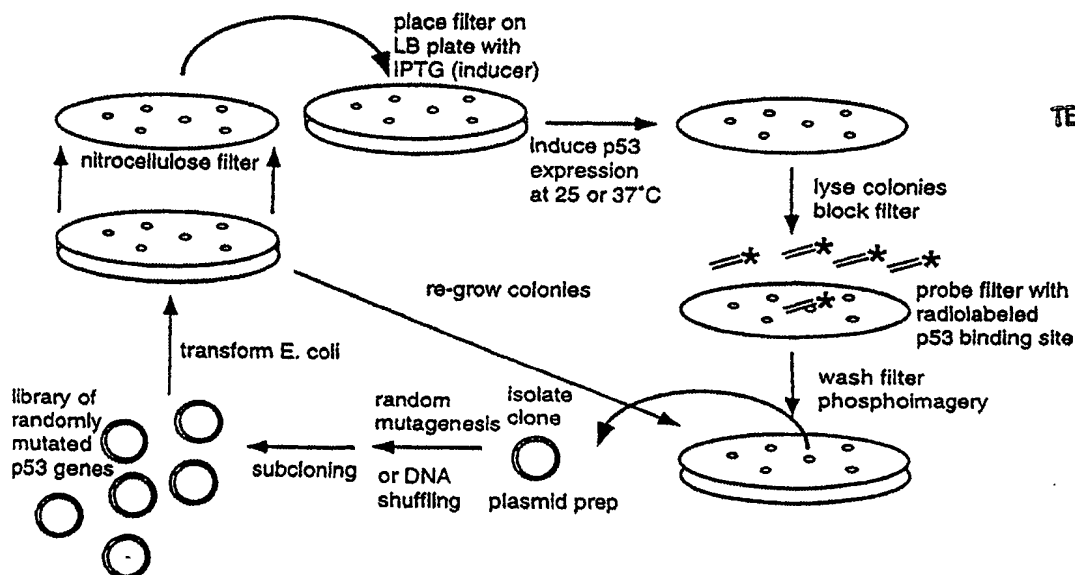
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C12N 15/10, C07K 14/47, C12Q 1/68		A3	(11) International Publication Number: <b>WO 00/22115</b>
			(43) International Publication Date: 20 April 2000 (20.04.00)
(21) International Application Number: PCT/US99/24072 (22) International Filing Date: 13 October 1999 (13.10.99) (30) Priority Data: 60/103,930 13 October 1998 (13.10.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/103,930 (CON) Filed on 13 October 1998 (13.10.98) (71) Applicants (for all designated States except US): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US). ADVANCED RESEARCH AND TECHNOLOGY INSTITUTE [US/US]; 501 North Morton St., Bloomington, IN 47404 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ELLINGTON, Andrew, D. [US/US]; 2106 Elton Road, Austin, TX 78703 (US). MATSUMURA, Ichiro [US/US]; Apartment 2, 709 W. 29th St., Austin, TX 78705 (US).			(74) Agent: HIGHLANDER, Steven, L.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 21 September 2000 (21.09.00)

(54) Title: ASSAYS FOR IDENTIFYING FUNCTIONAL ALTERATIONS IN THE P53 TUMOR SUPPRESSOR



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## (57) Abstract

The present invention provides for various screening assays which are amenable to high throughput formats and identify a variety of useful mutations in tumor suppressor genes such as p53. Such mutations include those that activate the molecule, increase thermostability, increase transcriptional activity and facilitate resistance to inhibitory molecules. Also provided are methods of screening for accessory proteins that interact with tumor suppressors in both inhibitory and activating fashions, as well as cleavable mutants of p53 that are activated by viral proteases.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24072

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/10 C07K14/47 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MATSUMURA ICHIRO ET AL: "In vitro evolution of thermostable p53 variants." PROTEIN SCIENCE APRIL, 1999, vol. 8, no. 4, April 1999 (1999-04), pages 731-740, XP000891282 ISSN: 0961-8368 the whole document	1-5, 17-44
P,X	XIRODIMAS DIMITRIS P ET AL: "Molecular evolution of the thermosensitive PAb1620 epitope of human p53 by DNA shuffling." JOURNAL OF BIOLOGICAL CHEMISTRY SEPT. 24, 1999, vol. 274, no. 39, pages 28042-28049, XP002133469 ISSN: 0021-9258 the whole document --- -/--	24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

17 March 2000

Date of mailing of the international search report

24.07.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

HORNIG H.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24072

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 17213 A (SLOAN KETTERING INST CANCER) 29 June 1995 (1995-06-29) the whole document ---	
A	WO 97 10843 A (WISTAR INST) 27 March 1997 (1997-03-27) the whole document ---	
A	WO 94 12202 A (UNIV DUNDEE ;LANE DAVID PHILIP (GB); HUPP THEODORE ROBERT (GB)) 9 June 1994 (1994-06-09) the whole document ---	
A	S. HANSEN ET AL.: "Modification of two distinct COOH-terminal domains is required for murine p53 activation by bacterial Hsp70" J. BIOL. CHEM., vol. 271, no. 48, 29 November 1996 (1996-11-29), pages 30922-30928, XP002133470 AM. SOC. BIOCHEM. MOL.BIOL.,INC.,BALTIMORE,US the whole document ---	
A	WO 95 06661 A (RES DEV FOUNDATION ;FUNG YUEN KAI (US)) 9 March 1995 (1995-03-09) the whole document ---	
A	WO 96 20207 A (RES DEV FOUNDATION ;FUNG YUEN KAI (US)) 4 July 1996 (1996-07-04) the whole document ---	
A	S. HANSEN ET AL.: "Allosteric regulation of the thermostability and DNA binding activity of human p53 by specific interacting proteins" J. BIOL. CHEM., vol. 271, no. 7, 16 February 1996 (1996-02-16), pages 3917-3924, XP002094746 AM. SOC. BIOCHEM. MOL.BIOL.,INC.,BALTIMORE,US the whole document ---	
A	EP 0 518 650 A (UNIV JOHNS HOPKINS ;PHARMAGENICS INC (US)) 16 December 1992 (1992-12-16) the whole document ---	
A	WO 97 14794 A (UNIV DUNDEE ;LANE DAVID PHILIP (GB); HUPP THEODORE ROBERT (GB)) 24 April 1997 (1997-04-24) the whole document ---	

-/--

# INTERNATIONAL SEARCH REPORT

International Application No

P. /US 99/24072

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 19367 A (JOLLA CANCER RES FOUND)  20 July 1995 (1995-07-20)  the whole document  -----</p>	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/24072

## Box I Observations where certain claims were found unsatisfactory (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-44, 81.

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## 1. Claims: 1-44,81

A method of identifying a thermostable p53 polypeptide comprising: (a) providing a population of polynucleotides encoding activated, mutated p53 polypeptides; (b) transforming host cells lacking an endogenous p53 polypeptide with said population of polynucleotides and culturing said host cells at elevated temperatures and under conditions permitting the expression of said mutated, activated p53 polypeptides; (c) screening said mutated p53 polypeptides for p53 DNA binding activity; and (d) comparing the DNA binding of step (c) with the DNA binding of an activated p53 polypeptide produced at said elevated temperatures, wherein increased binding of said activated, mutated p53 polypeptide, as compared to an activated p53 polypeptide, identifies a thermostable p53 polypeptide; said method, wherein said activated p53 polypeptide (i) contains a truncation of a C-terminal portion of wild-type p53, wherein said portion is a deletion of residue 360, (ii) wherein said activated p53 polypeptide comprises a first point mutation selected from the group consisting of K-3, R-23, S-54, N-106, A-123, R-137, T-159, -160, D-268, S-268, T-332, G-339 and V-344; a thermostable p53 polypeptide comprising a first point mutation, wherein said mutation is selected from the group consisting of V-133, Y-239, D-268, V-336, P-364, V-62, T-116, P-166, T-270, S-88, I-157, V-344, G-42, S-268, K-51, G-326, E-207, S-212, H-264, A-203, L-80, A-30, K-56, N-106, R-115, S-227, M-344, Q-45, A-102, S-191, T-322, A-31, G-49, T-183, I-264 and V-346; said polypeptide further comprising a second, third, fourth and fifth point mutation; a polynucleotide sequence encoding said thermostable p53 polypeptide comprising a first point mutation;

## 2. Claims: 45-62,82-85

A method of identifying an activated p53 polypeptide comprising: (a) providing a population of polynucleotides encoding mutated p53 polypeptides; (b) transforming bacterial host cells lacking an endogenous p53 polypeptide with said population of polynucleotides and culturing said host cells under conditions permitting the expression of said mutated p53 polypeptides; (c) screening said mutated p53 polypeptides for p53 DNA binding activity; and (d) comparing the DNA binding of step (c) with the DNA binding of wild-type p53 polypeptide, wherein increased binding of said mutated p53 polypeptide, as compared to wild-type p53, identifies an activated p53 polypeptide; an activated p53 polypeptide comprising a deletion of residue 360; but retaining sequences flanking residue 360; an activated p53 polypeptide comprising a first point mutation when compared to wild-type p53, wherein said point mutation are selected from the group consisting of K-3, R-23, S-54, N-106, A-123, R-137, T-159, T-160, D-268, S-268, T-332, G-339 and V-344;

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

said polypeptide, wherein said activated p53 polypeptide comprises a second and third mutation; said p53 polypeptide comprising an insertion or internal deletion when compared to wild-type p53; wherein said insertion is at residue 317 and said deletion is at residue 365; a polynucleotide sequence encoding said activated p53 polypeptide;

## 3. Claims: 63-64

A method of identifying an activator/inhibitor of p53 DNA binding comprising: (a) providing a plurality of cDNAs and a polynucleotide encoding a full length p53 polypeptide; (b) transforming host cells lacking an endogenous p53 polypeptide with said cDNAs and said p53-encoding polynucleotide, and culturing said host cells under conditions permitting the expression of products encoded by said cDNAs and full length p53 polypeptide; and (c) screening said products encoded by said cDNAs for p53 DNA binding activity or loss of p53 DNA binding activity;

## 4. Claim : 65

A method of identifying SV40 resistant p53 polypeptides comprising: (a) providing a polynucleotide encoding the SV40 large T antigen and a population of polynucleotides encoding activated, mutated p53 polypeptides; (b) transforming host cells lacking an endogenous p53 polypeptide with said SV40 large T antigen-encoding polynucleotide and said p53-encoding polynucleotides, and culturing said host cells under conditions permitting the expression of said SV40 large T antigen and said mutated, activated p53 polypeptides; (c) screening said mutated, activated p53 polypeptides for p53 DNA binding activity; and (d) comparing the DNA binding of step (c) with the DNA binding of an activated p53 polypeptide coexpressed with SV40 large T antigen, wherein increased binding of a mutated, activated p53 polypeptide, as compared to activated p53, identifies an SV40 resistant p53 polypeptide;

## 5. Claims: 66-69

A method for identifying a p53 polypeptide with increased transcriptional activity comprising: (a) providing a population of mutated p53 polypeptides; (b) transforming host cells lacking an endogenous p53 polypeptide with said population of mutated p53 molecules, wherein said host cells contain a reporter gene driven by a p53-dependent promoter; (c) screening said host cells for expression of the gene product encoded by said reporter gene; and (d) comparing the expression of said reporter gene in step (c) with the expression of said reporter gene by wild-type p53, wherein an increase in the expression of said reporter gene in cells

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

expressing said mutated p53 molecule, as compared to cells expressing wild-type p53, indicates a p53 polypeptide having increased transcriptional activity;

## 6. Claims: 70-80

A mutant p53 polypeptide containing an HIV-1 protease site upstream of the carboxy-terminal region thereof, whereupon cleavage by HIV-1 protease, said p53 molecule is activated; said mutant p53 polypeptide, wherein the cleavage site is VSFNFPQITL; wherein said cleavage site is inserted immediately after amino acid residue 359; wherein said amino acid sequence VSFNFPQITL is substituted for amino acid residues 360-369 of the wild-type p53 amino acid sequence; an infectious retrovirus, the RNA which encodes said mutant p53 polypeptide; a method of inhibiting HIV-1 replication in a cell infected with HIV-1 comprising contacting said cell with an infectious retrovirus, the RNA of which encodes a mutant p53 polypeptide containing an HIV-1 protease cleavage site upstream of the carboxy-terminal region thereof, whereupon cleavage by HIV-1 protease, said p53 molecule is activated;



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/US 99/24072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9517213 A	29-06-1995	AU 1440695 A	10-07-1995
W0 9710843 A	27-03-1997	US 5847083 A	08-12-1998
		AU 7242996 A	09-04-1997
W0 9412202 A	09-06-1994	AT 180673 T	15-06-1999
		AU 680216 B	24-07-1997
		AU 5533194 A	22-06-1994
		CA 2150265 A	09-06-1994
		DE 69325180 D	08-07-1999
		DE 69325180 T	02-12-1999
		EP 0675729 A	11-10-1995
		ES 2134336 T	01-10-1999
		GR 3030900 T	30-11-1999
		JP 8505607 T	18-06-1996
W0 9506661 A	09-03-1995	AU 692793 B	18-06-1998
		AU 7642694 A	22-03-1995
		CA 2170605 A	09-03-1995
		CN 1133595 A	16-10-1996
		EP 0716660 A	19-06-1996
		JP 9502183 T	04-03-1997
		US 5969120 A	19-10-1999
		ZA 9406595 A	28-02-1996
W0 9620207 A	04-07-1996	US 5969120 A	19-10-1999
		AU 700610 B	07-01-1999
		AU 4745196 A	19-07-1996
		CA 2208706 A	04-07-1996
		CN 1171113 A	21-01-1998
		EP 0808323 A	26-11-1997
		JP 10511553 T	10-11-1998
EP 0518650 A	16-12-1992	US 5362623 A	08-11-1994
		AT 147512 T	15-01-1997
		AU 666479 B	15-02-1996
		AU 1820092 A	17-12-1992
		CA 2070979 A	15-12-1992
		DE 69216478 D	20-02-1997
		DE 69216478 T	19-02-1998
		DK 518650 T	27-01-1997
		ES 2097878 T	16-04-1997
		GR 3022473 T	31-05-1997
		JP 6078798 A	22-03-1994
		US 5955263 A	21-09-1999
W0 9714794 A	24-04-1997	AU 7317496 A	07-05-1997
		EP 0859839 A	26-08-1998
W0 9519367 A	20-07-1995	US 5484710 A	16-01-1996
		US 5659024 A	19-08-1997
		US 5908750 A	01-06-1999

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 14 July 1999 (14.07.99)	
<b>International application No.</b> PCT/US98/23992	<b>Applicant's or agent's file reference</b> 5780-01-TMC
<b>International filing date</b> (day/month/year) 10 November 1998 (10.11.98)	<b>Priority date</b> (day/month/year) 17 November 1997 (17.11.97)
<b>Applicant</b> BIAN, Junhui et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

19 May 1999 (19.05.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  R. Forax Telephone No.: (41-22) 338.83.38
--	---

NOTED

PATENT COOPERATION TREA. 1

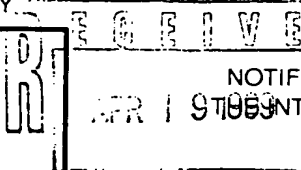
APR 19 1999

R. ARMSTRONG INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

WARNER-LAMBERT COMPANY  
Attn. RYAN, A.  
201 Tabor Road  
Morris Plains, New Jersey 07950  
UNITED STATES OF AMERICA



NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

MP PATENT DEPT. (PCT Rule 44.1)

Date of mailing  
(day/month/year)

13/04/1999

Applicant's or agent's file reference

5780-01-TMC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 98/ 23992

International filing date  
(day/month/year)

10/11/1998

Applicant

WARNER-LAMBERT COMPANY et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Sandra De Jong-van Dam

Express Mail No. EJ67605310IUS  
PD-5780-01-TMC

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>5780-01-TMC</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 98/23992</b>	International filing date (day/month/year) <b>10/11/1998</b>	(Earliest) Priority Date (day/month/year) <b>17/11/1997</b>
Applicant <b>WARNER-LAMBERT COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23992

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C07K14/47 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17213 A (SLOAN KETTERING INST CANCER) 29 June 1995	1
A	see page 21 - page 26 see figures 1A and 1B	2-4
X	BIAN ET AL: "Characterisation of a putative p53 binding site in the promoter of the mouse tissue inhibitor of metalloproteinases-3 (TIMP-3) gene: TIMP-3 is not a p53 target gene" CARCINOGENESIS, vol. 17, no. 12, 1996, pages 2559-2562, XP002098171	2, 3
A	cited in the application see abstract see page 2560, right-hand column, paragraph 2 - page 2561, left-hand column, line 4	1, 4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 March 1999

Date of mailing of the international search report

13/04/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23992

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT.

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
A	KAGHAD ET AL: "Monoallelically Expressed Gene Related to p53 at 1p36, a Region Frequently Deleted in Neuroblastoma and Other Human Cancers" CELL, vol. 90, 22 August 1997, pages 809-819, XP002098172 cited in the application see abstract -----	1
A	EL-DEIRY ET AL: "Definition of a consensus binding site for p53" NATURE GENETICS, vol. 1, 1992, pages 45-49, XP002098173 cited in the application -----	2-4
A	WO 96 01907 A (SQUIBB BRISTOL MYERS CO) 25 January 1996 see page 38, SEQ ID NO.:3 -----	4
P,X	BIAN AND SUN: "p53CP, a putative p53 competing protein that specifically binds to the consensus p53 DNA binding sites: A third member of the p53 family?" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, vol. 94, December 1997, pages 14753-14758, XP002098174 see the whole document -----	1-4



# INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9517213	A	29-06-1995	AU	1440695 A	10-07-1995
WO 9601907	A	25-01-1996	US	5667987 A	16-09-1997
			EP	0804609 A	05-11-1997